AMENDMENTS TO THE SPECIFICATION

IN THE WRITTEN DESCRIPTION:

Please replace the paragraph starting at page 3, line 5 with the following amended paragraph.

B1

With regard to glucose metabolism, the following reports have been available. In an experiment using skeletal muscles, adenosine lowers the insulin sensitivity due to an agonistic action on the A1 receptor suppressing the glucose uptake while an A1 receptor antagonist increases the insulin sensitivity (Challis, R. A., Biochem., J., 221, 915-917, 1984; Challis, R. A., Eur. J. Pharmacol., 226, 121-128, 1992). In adipocytes, adenosine enhances the sensitivity of insulin via an A1 receptor, whereby glucose uptake is promoted (Vannucci, S. J., Biochem. J., 288, 325-330, 1992). Further, WO 95/18128 and WO 98/03507 disclose a therapeutic agent for diabetes mellitus comprising an A1 receptor antagonist. Thus, there have been many reports on an A1 receptor. With regard to an adenosine A2 receptor, there is a simple description in WO 97/01551 suggesting a therapeutic agent for diabetes mellitus comprising the A2a receptor antagonist although any ground is not mentioned at all. In TIPS., 14, 360-366, 1993, participation of the adenosine A2 receptor in the promotion of gluconeogenesis in hepatic cells is suggested but there is no specific description

at all. On the contrary, WO 98/01459 describes a therapeutic agent for diabetes mellitus comprising the A2 receptor agonist but there is no description of the adenosine A2 receptor antagonist at all. As such, the positioning of the adenosine A2 receptor antagonist as a therapeutic agent for diabetes mellitus has been in a chaotic state.

B1

Please replace the paragraph starting at page 11, line 10 with the following amended paragraph.

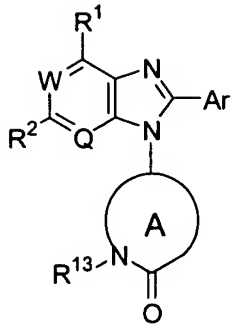
the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is amino, R^2 is a C2 alkynyl group which is substituted with ~~hydroxyl group and~~ a hydroxy-C4-C6 cycloalkyl group, R^3 is a C3 alkenyl group, and Ar is a phenyl substituted with a halogen atom; and

B2

Please replace the paragraph starting at page 21, line 11 with the following amended paragraph.

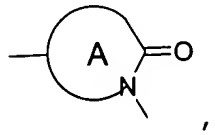
B3 NE

a process for producing an imidazopyridine compound (C3), a salt thereof or hydrates thereof represented by the formula:



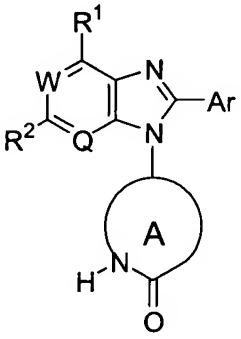
(C3)

(wherein R^{13} means a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group, or an optionally substituted C3-C6 cycloalkyl group; and R^1, the formula:



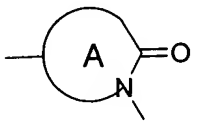
,

R^2, Ar, Q and W have the same meanings as defined above, respectively), which comprises alkylating an imidazopyridine compound (C2) represented by the following formula:



(C2)

(wherein R^1 represents 1) hydrogen, 2) hydroxyl, 3) a halogen atom, 4) an optionally substituted C1-C8 alkyl group or 5) formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen, a C1-C8 alkyl group or a C3-C8 cycloalkyl group, or a C2-C5 saturated cyclic amino group which is formed with a nitrogen atom to which they bind, whereupon this ring may contain oxygen, sulfur or nitrogen other than the nitrogen atom and may be substituted with a C1-C4 alkyl group which may be substituted with a halogen atom; the formula:



represents dihydrooxopyridinyl or -pyrimidyl, or ~~dihydro-~~ dihydroxo- or ~~tetrahydropyrazinyl~~ tetrahydroxopyrazinyl; and R^2, Ar, Q and W have the same meanings as defined above, respectively.

Please replace the paragraph starting at page 26, line 3 with the following amended paragraph.

The acyl group in the definition of R^2 includes aliphatic saturated monocarboxylic acid-derived groups such as acetyl group, propionyl group, butyryl group, valeryl group, isovaleryl group and pivaloyl group; aliphatic unsaturated carboxylic acid-derived groups such as acryloyl group, ~~propionyl~~ propioloyl

group, methacryloyl group, crotonyl group and isocrotonyl group; carbon-cyclic-carboxylic acid-derived groups such as benzoyl group, naphthoyl group, toluoyl group, hydroatropoyl group, atropoyl group and cinnamoyl group; heterocyclic carboxylic acid-derived groups such as furoyl group, thenoyl group, nicotinoyl group and isonicotinoyl group; hydroxycarboxylic acid- or alkoxycarboxylic acid-derived groups such as glycoloyl group, lactoyl group, glyceroyl group, tropoyl group, ~~benzyloyl~~ benziloyl group, salicyloyl group, anisoyl group, vanilloyl group, piperonyloyl group, galloyl group; or groups derived from various amino acids.

Please replace the paragraph starting at page 28, line 18 with the following amended paragraph.

In the definition of ~~R^3, R^4~~ R^4, R^5, R^6 and R^7, the term "C2-C5 saturated cyclic amino group which is formed with a nitrogen atom to which they bind" refers to aziridine, azetidine, pyrrolidine, piperidine, piperazine, homopiperazine, morpholine or thiomorpholine. These rings may be substituted with a C1-C4 alkyl group which may be substituted with a halogen atom.

Please replace the paragraph starting at page 38, line 2 with the following amended paragraph.

B6

In this case, when R^2 is i) a C2-C8 alkynyl group which may be substituted with a halogen atom, hydroxyl, a C1-C4 alkyl group or a C3-C6 cycloalkyl group, ii) a C3-C8 alkenyl group which may be substituted with a halogen atom, hydroxyl or a C1-C4 alkyl group or iii) a C1-C8 alkyl group which may be substituted with a halogen atom, hydroxyl or a C1-C4 alkyl group, R^3 represents 1) a C3-C8 alkynyl group which may be substituted with a halogen atom, hydroxyl or a C1-C4 alkyl group, 2) a C3-C8 alkenyl group which may be substituted with a halogen atom, hydroxyl or a C1-C4 alkyl group, 5) an optionally substituted heteroaryl group, 6) a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, 7) a dihydroxopyrimidyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally

B6

substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) a C3-C6 cycloalkyl group, or 8) a dihydroxo- or tetrahydrodioxopyrazinyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) a C3-C6 cycloalkyl group, preferably 5) an optionally substituted heteroaryl group, 6) a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, 7) a dihydroxopyrimidyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group ~~which may have a substituent group~~ or b-3) a C3-C6 cycloalkyl group or 8) a dihydroxo- or tetrahydrodioxopyrazinyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and

B6

whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) a C3-C6 cycloalkyl group, more preferably 6) a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, 7) a dihydroxopyrimidyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) a C3-C6 cycloalkyl group, or 8) a dihydroxo- or tetrahydrodioxopyrazinyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) a C3-C6 cycloalkyl group, further more preferably 6) a 1,2-

B6

dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, or 7) a dihydroxopyrimidyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) a C3-C6 cycloalkyl group, further preferably 6) a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, still further preferably 6) a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally

B6 protected carboxyl group, and most preferably a 1,2-dihydro-2-oxopyridyl group or a 1-methyl-1,2-dihydro-2-oxopyridyl group.

Please replace the paragraph starting at page 41, line 21 with the following amended paragraph.

B7 Ar represents 1) an optionally substituted aryl group, 2) an optionally substituted heteroaryl group, 3) an oxopyridyl group which may be substituted with a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with a C1-C6 alkyl group or a C3-C6 cycloalkyl group or 4) an oxopyrimidyl group which may be substituted with a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with a C1-C6 alkyl group or a C3-C6 cycloalkyl group, ~~preferably 1) an optionally substituted aryl group, 2) an optionally substituted heteroaryl group, 3) an oxopyridyl group which may be substituted with a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with a C1-C6 alkyl group or a C3-C6 cycloalkyl group or 4) an oxopyrimidyl group which may be substituted with a halogen atom or a C1-C6 alkyl group and whose nitrogen atom is further substituted with a C1-C6 alkyl group or a C3-C6 cycloalkyl group, more~~ preferably 1) an optionally substituted aryl group, 2) an optionally substituted heteroaryl group or 3) an oxopyridyl group which may be substituted with a halogen atom or a C1-C6 alkyl group and

whose nitrogen atom is further substituted with a C1-C6 alkyl group or a C3-C6 cycloalkyl group, further preferably 1) an optionally substituted aryl group or 2) an optionally substituted heteroaryl group, still further preferably an optionally substituted aryl group, and most preferably an optionally substituted phenyl group.

Please replace the paragraph starting at page 52, line 6 with the following amended paragraph.

This step can be finished in the previous step B2 depending on the conditions for substitution with the amino derivative in the step B2, and in such case, this step is omitted.

Step B4: This step is the step of dehydration condensation of ~~the amino group at the 4-position with its adjacent aldehyde at the 5-position on the pyrimidine ring~~ the amino groups at the adjacent 4 and 5-position on the pyrimidine ring with an aldehyde to form an imidazole ring thereby producing a purine derivative 5.

Please replace the paragraph starting at page 83, line 9 with the following amended paragraph.

B9

5) N1-[4-Chloro-6-(2-~~propylamino~~butynylamino)-5-pyrimidinyl]-3-fluorobenzamide

5.9 ml of 3-fluorobenzoyl chloride was added dropwise to a solution of 48.8 mmol N4-(2-~~propinyl~~butynyl)-6-chloro-4,5-pyrimidine diamine in 50 ml pyridine, and this mixture was stirred for 15 minutes in a nitrogen atmosphere at 0 °C and further stirred for 30 minutes at room temperature. Water was added to the reaction solution at room temperature, and the resulting mixture was extracted with ethyl acetate. The organic layer was successively washed with water and brine, and the whole aqueous layer was extracted again with ethyl acetate. The whole organic layer was dried over magnesium sulfate and filtered, followed by evaporating the solvent to give crystals. The resulting crystals were washed with diethyl ether and collected by filtration, to give 5.64 g of N1-[4-chloro-6-(2-~~propinylamino~~butynylamino)-5-pyrimidinyl]-3-fluorobenzamide as white crystals.

^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.07 (1H, t, J=2.4Hz), 4.12-4.14 (2H, m), 7.45-7.50 (1H, m), 7.58-7.63 (1H, m), 7.80-7.87 (2H, m), 8.05-8.08 (1H, m), 8.34 (1H, s).

Please replace the paragraph starting at page 84, line 3 with the following amended paragraph.

B10

Then, a suspension of 5.64 g N1-[4-chloro-6-(2-propinylamino)-5-pyrimidinyl]-3-fluorobenzamide in 56 ml phosphorus oxychloride was stirred at 120 °C for 7 hours. The phosphorus oxychloride was evaporated from the reaction solution, and ice-water was added to the residue. This mixture was neutralized with sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The aqueous layer was filtered through Celite, and the filtrate was extracted again with ethyl acetate, and the whole organic layer was dried over magnesium sulfate. The residue was purified by silica gel short-column chromatography, and the resulting crystals were washed with diethyl ether and collected by filtration, to give 6-chloro-8-(3-fluorophenyl)-9-(2-~~propinyl~~butynyl)-9H-purine (2.08 g, 35 %) as pale brown crystals.

^{1}H NMR (400MHz,DMSO-d_6) δppm 3.56(1H,t,J=2.6Hz), 3.40(2H,d,J=2.4Hz), 7.53-7.58 (1H, m), 7.71-7.76 (1H, m), 7.82-7.87 (1H, m), 8.89 (1H, s).

MS m/e (ESI): 287(MH^+).

Please replace the paragraph starting at page 86, line 19 with the following amended paragraph.

B11

10 % hydrous palladium-carbon (10 mg) and p-toluenesulfonic acid monohydrate (12 mg, 0.063 mmol) were added to a solution of ~~the compound~~ 4-[9-(6-allyloxypyridine-3-yl)amino-8-(3-fluorophenyl)-9H-purin-2-yl]-2-methylbut-3-yn-2-ol synthesized in the same methods as in Examples 7 and 10 (90 mg, 0.202 mmol) in ethanol (10 ml)-water (2 ml), and the mixture was heated under reflux. After 30 minutes, p-toluenesulfonic acid monohydrate (110 mg, 0.578 mmol) was added thereto, and 1.5 hours thereafter, 10 % hydrous palladium-carbon (10 mg) and p-toluenesulfonic acid monohydrate (100 mg, 0.526 mmol) were additionally added thereto, and the mixture was heated under reflux for 3 days. After the palladium-carbon was filtered off, the filtrate was diluted with ethyl acetate and washed with a saturated aqueous ammonium chloride solution (x1). After extraction with 1N aqueous sodium hydroxide (x1), the aqueous layer was neutralized with 5N hydrochloric acid. The aqueous layer was extracted with ethyl acetate (x1), then dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in methanol-5N hydrochloric acid (3 drops) and concentrated. The residue was crystallized from methanol/ethyl acetate/diethyl ether, and the solid was collected by filtration

and washed with diethyl ether, to give the title compound 27 (18 mg, 20 %) as a pale yellow solid.

B11

^{1}H NMR (400MHz,DMSO-d_6) δppm 1.45 (6H, s), 6.46 (1H, d, J=9.6Hz), 7.31-7.38 (1H, m), 7.40-7.47 (2H, m), 7.47-7.56 (2H,m), 7.73 (1H, d, J = 2.8 Hz).

MS m/e (ESI): 405 (MH^+).

Please replace the paragraph starting at page 94, line 18 with the following amended paragraph.

B12

Example 30 2-[5-[6-Amino-8-(~~2-furyl~~3-fluorophenyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] acetic acid

Please replace the paragraph starting at page 95, line 1 with the following amended paragraph.

B13

5N aqueous sodium hydroxide (2.0 ml, 10 mmol) was added to a solution, in methanol (6 ml)/tetrahydrofuran (6 ml)/water (10 ml), of ethyl 2-[5-[6-amino-8-(~~2-furyl~~3-fluorophenyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] acetate (600 mg, 1.47 mmol) synthesized in the same manner as in Example 21, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated, dissolved in water and neutralized with 5N hydrochloric acid. The resulting crystals were collected by filtration and washed with water, to give the title compound (252 mg, 57 %) as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 4.61 (2H, s), 6.53 (1H, d, J = 9.6 Hz), 7.29-7.35 (1H, m), 7.45-7.52 (5H, m), 7.55 (1H, dd, J = 2.8, 9.6 Hz), 8.05 (1H, d, J = 2.8 Hz), 8.16 (1H, s)

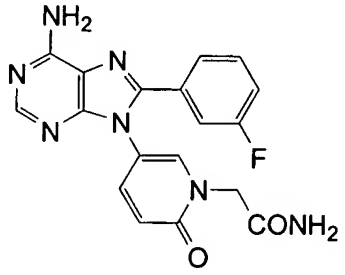
MS m/e (ESI) 381 (MH^+).

Please replace the paragraph starting at page 95, line 15 with the following amended paragraph.

Example 31 2-[5-[6-Amino-8-(~~2-furyl~~3-fluorophenyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] butyric acid

Please replace the paragraph starting at page 96, line 8 with the following amended paragraph.

Example 32 2-[5-[6-Amino-8-(~~2-furyl~~3-fluorophenyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] acetamide



A suspension of 2-[5-[6-amino-8-(~~2-furyl~~3fluorophenyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl]acetic acid (150 mg, 0.394 mmol), 1-hydroxybenzotriazole (180 mg, 1.18 mmol), ammonium chloride (105 mg, 1.96 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (184 mg, 1.19 mmol) and triethylamine (0.28 ml, 2.00 mmol) in N,N-dimethylformamide (3

ml) was stirred at room temperature for 20 hours. The reaction solution was concentrated, and the residue was subjected to silica gel column chromatography (eluting solvent: dichloromethane, dichloromethane/methanol=20:1, 10:1, 4:1). The crude product was suspended in ethanol, and the solid was collected by filtration and washed with ethanol, to give the title compound (96 mg, 64 %) as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 4.51 (2H, s), 6.48 (1H, d, J = 9.6 Hz), 7.21 (1H, br s), 7.28-7.34 (1H, m), 7.45-7.54 (6H, m), 7.62 (1H, br s), 7.98 (1H, d, J = 2.8 Hz), 8.16 (1H, s)

MS m/e (ESI) 380 (MH^+).

Please replace the paragraph starting at page 114, line 26 with the following amended paragraph.

(~~5-4~~5-5) 5-[6-Chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

Please replace the paragraph starting at page 124, line 20 with the following amended paragraph.

Example 54 N-[9-(6-Chloro-3-pyridazinyl)-8-(3-fluorophenyl)-9H-~~9-purinyl~~6-purinyl]-N,N-dimethylamine

Please replace the paragraph starting at page 130, line 2 with the following amended paragraph.

B18

N-[9-(6-Chloro-3-pyridazinyl)-8-(3-fluorophenyl)-9H-6-purinyl]-N,N-dimethylamine (50 mg, 0.18 mmol) in Example 54 was dissolved in 5 ml anhydrous methanol, and sodium methoxide (15 mg, 0.28 mmol) was added thereto and heated under reflux for 2 hours. The reaction solution was cooled, evaporated and suspended in water, and the precipitated solid were separated by filtration, to give the title compound (35 mg, 52 %) as a colorless solid.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 3.40 (3H,s), 4.04 (3H, s), 4.15 (3H,s), 6.92-6.98 (1H, m), 7.23 (1H, d, J = 9.5 Hz), 7.28-7.34 (1H, m), 7.93-7.97 (1H, m), 8.0-8.06 (1H, m), 8.91 (1H, d, J = 9.5 Hz), 8.93 (1H,s).

Please replace the paragraph starting at page 131, line 10 with the following amended paragraph.

B19

~~The~~ Using 5-{6-amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclobutyl)-1-ethynyl]-9H-9-purinyl}-1,2-dihydro-2-pyridinone as a starting material, the title compound was obtained by treatment in the same manner as in Example 21.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 1.75-1.83 (2H, m), 2.21-2.30 (2H,m), 2.50-2.60(2H,m), 3.54(3H,s), 6.10(2H,bs),

6.56(2H,d,J=9.7Hz), 7.07 (1H,dd, J=2.9,9.7Hz), 7.08-7.14 (1H, m), 7.26-7.38(3H,m), 7.50 (1H, d, J = 2.4Hz).

MS m/e (FAB) 431 (MH^+).